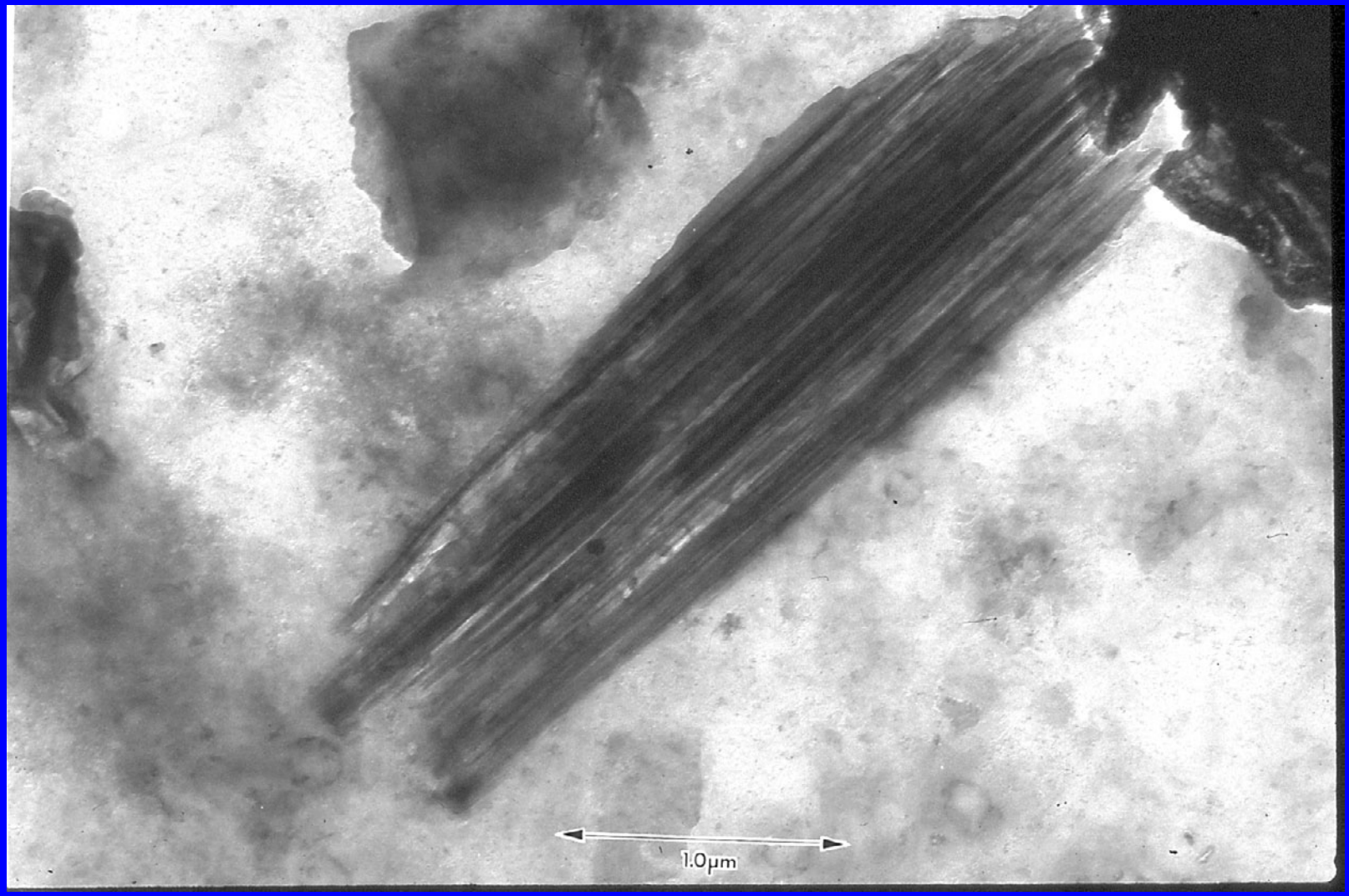
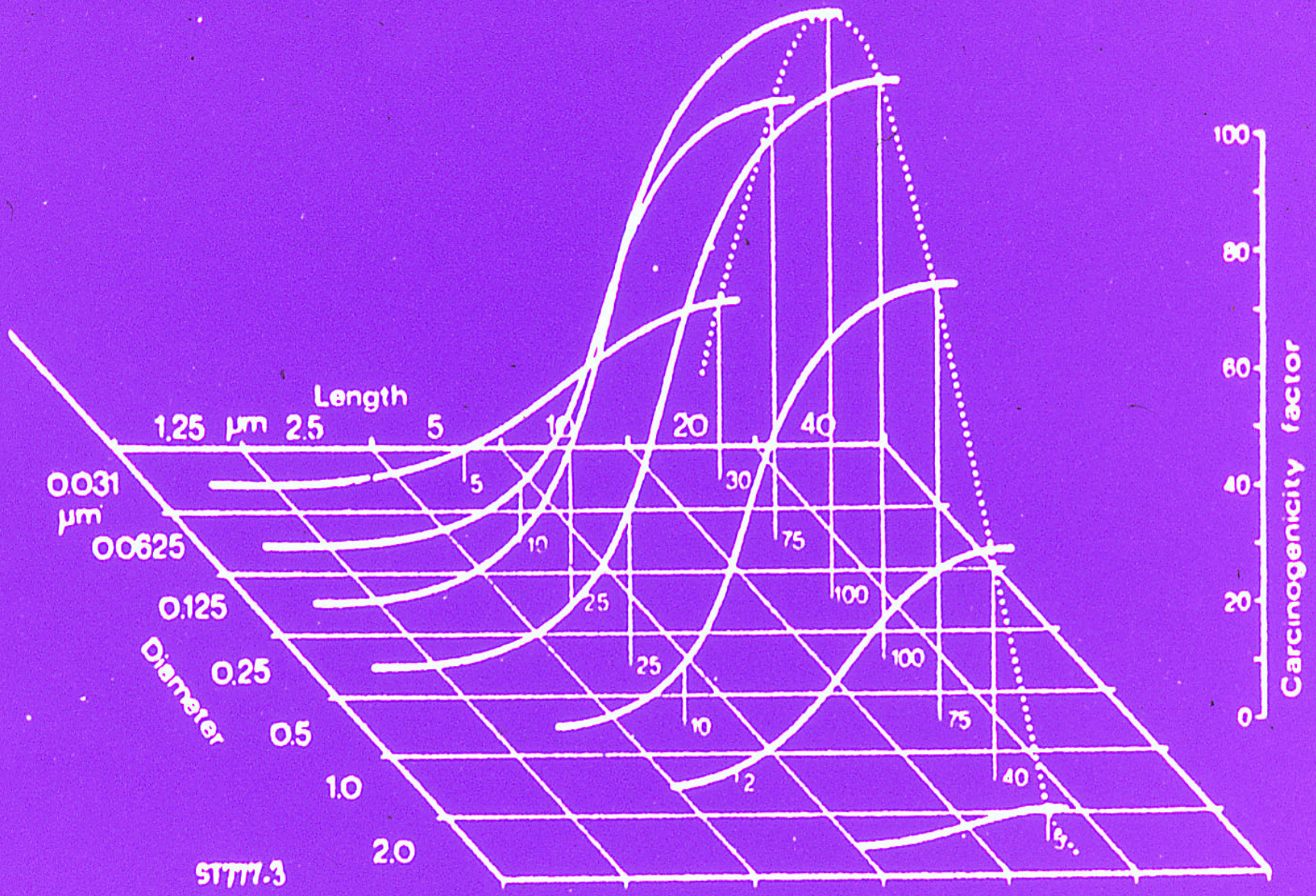
Eureka!

ferroactinolite fibers were dissolving and splitting longitudinally while residing in rat lung tissues over time.

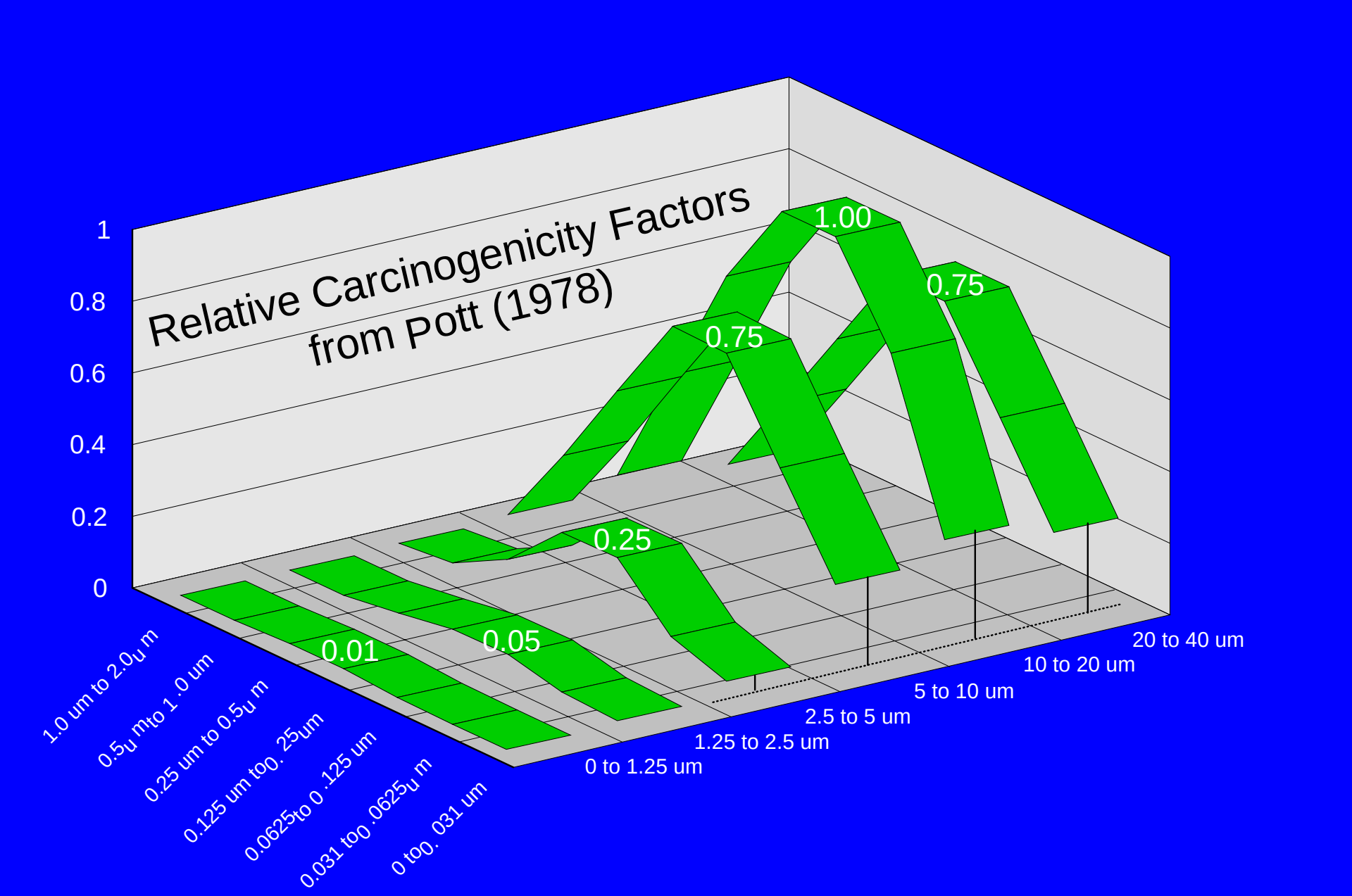


Anthophyllite in human lung



Conceptual Model for Carcinogenic Potency - Pott, 1978

(This three-dimensional model requires the fibre sizes of a sample to be divided into numerous categories. The size categories include three parameters: length, diameter and the length/diameter ratio)

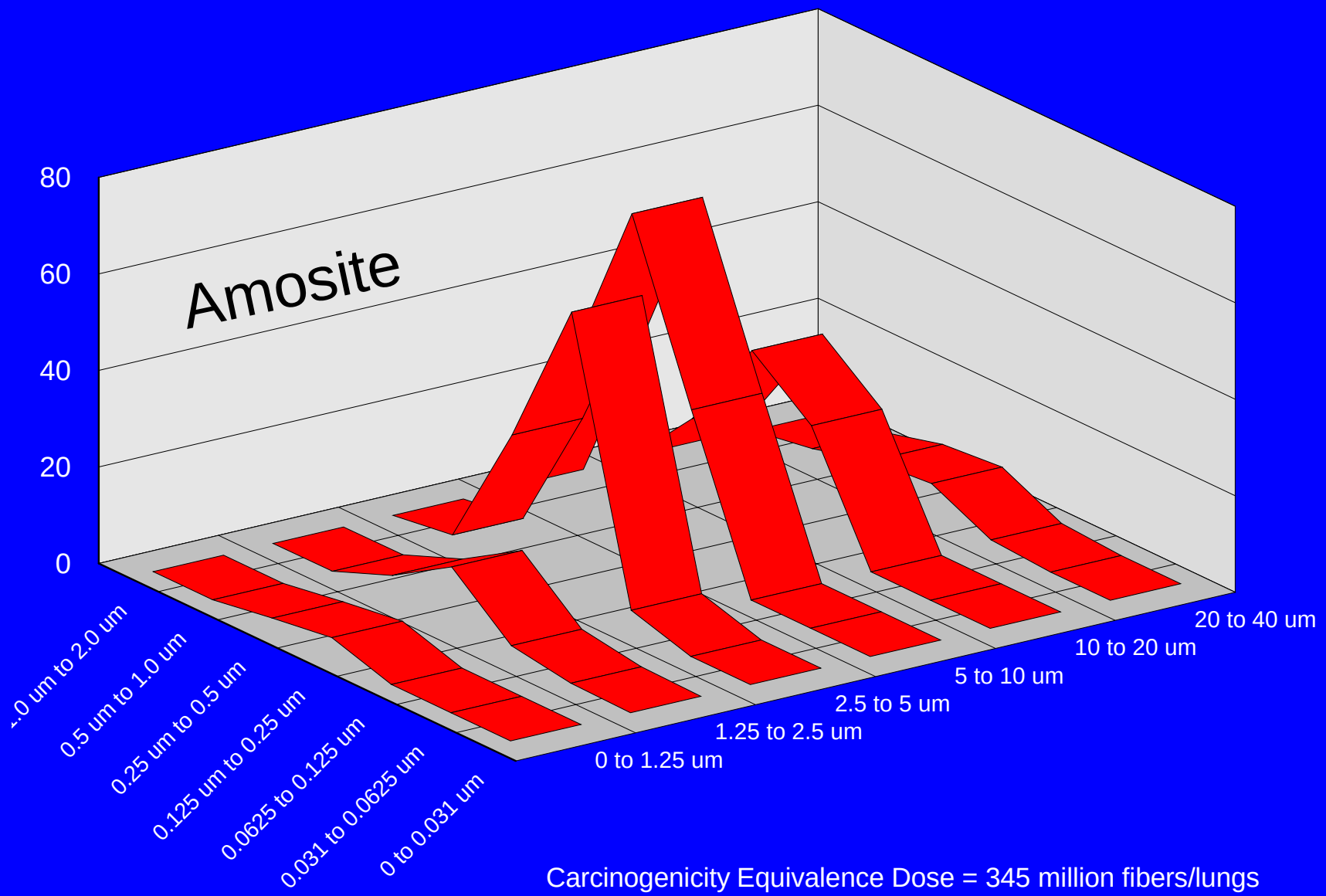


RCF = fraction of maximum potency/fiber

Carcinogenicity Equivalence Dose (CED)

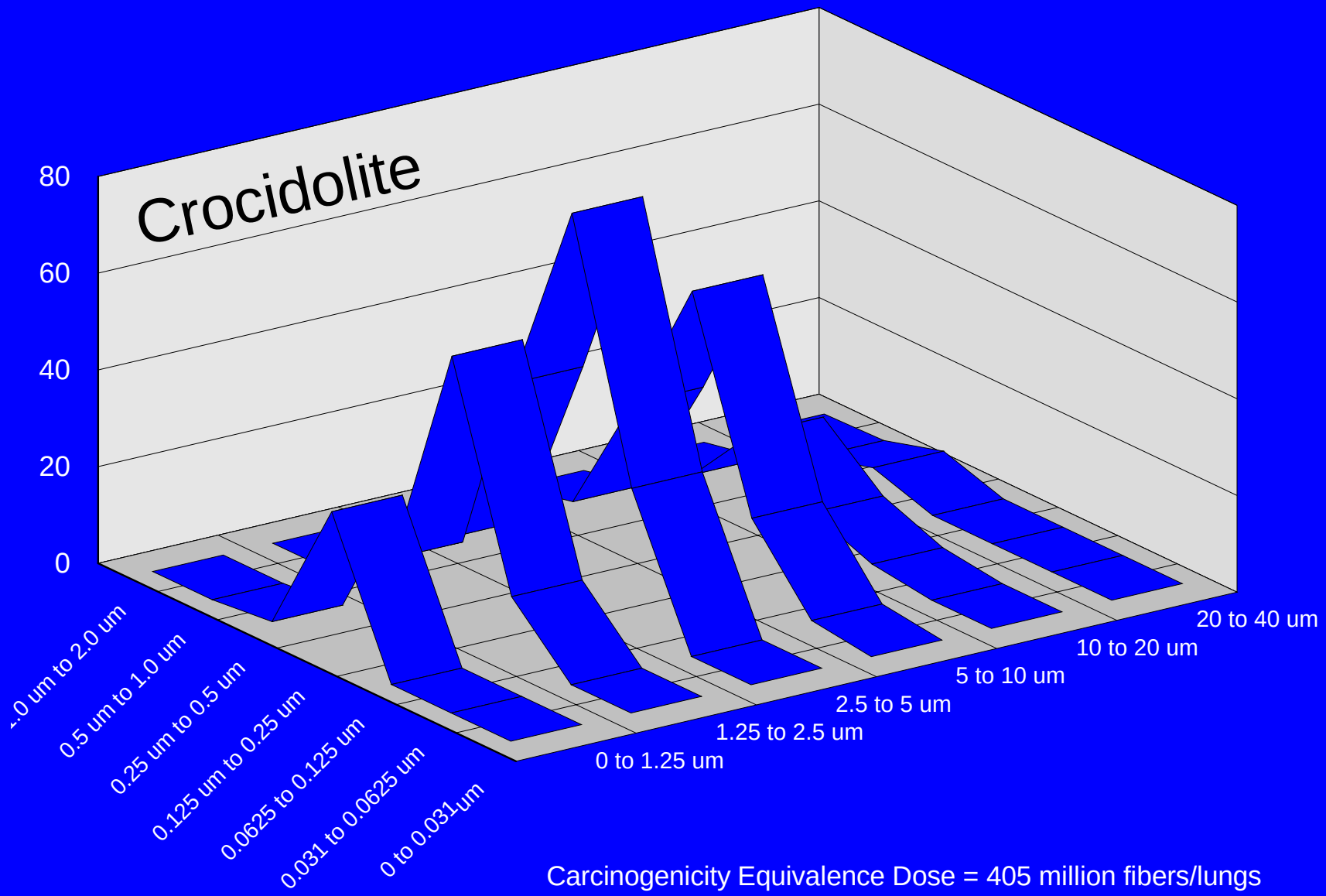
- A CED is the number of most potent fiber equivalents in the lung or pleura that results in a defined % of tumors.
- CED = $\Sigma(RCF_{i,j})\,(C_{i,j})$, where $C_{i,j}$ = # fibers/organ, RCF is the relative carcinogenicity factor (0 - 1), and i,j defines each of i⍙j length/width categories.
- The smaller the sample's CED, the greater the predicted potency for individual fibers.
- If amphiboles have equipotent fibers within specified size and shape ranges and the associated RCF values are reasonable, CEDs should be similar.

Rat Intratracheal Instillation



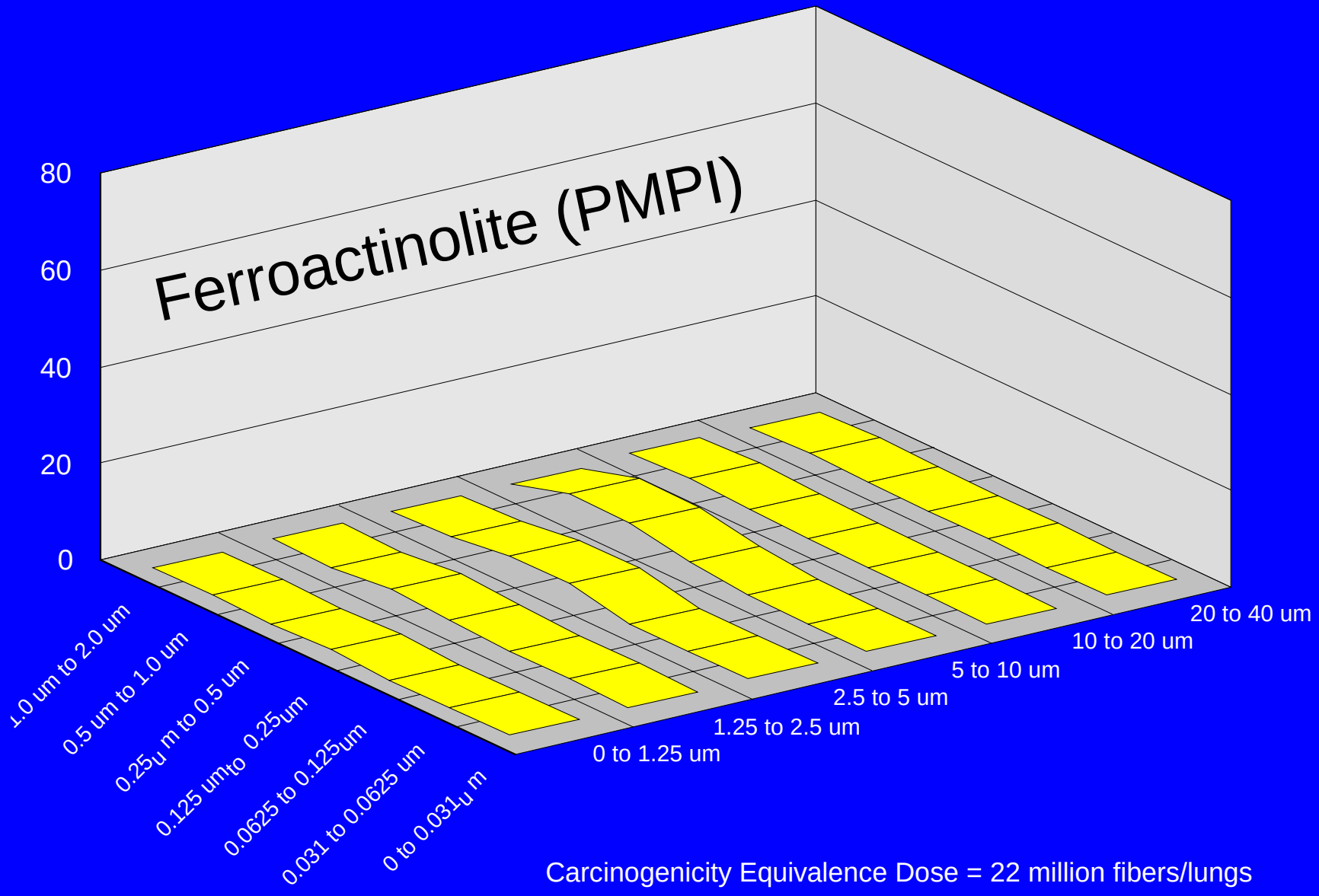
Carcinogenicity Equivalence Dose = 345 million fibers/lungs

Rat Intratracheal Instillation



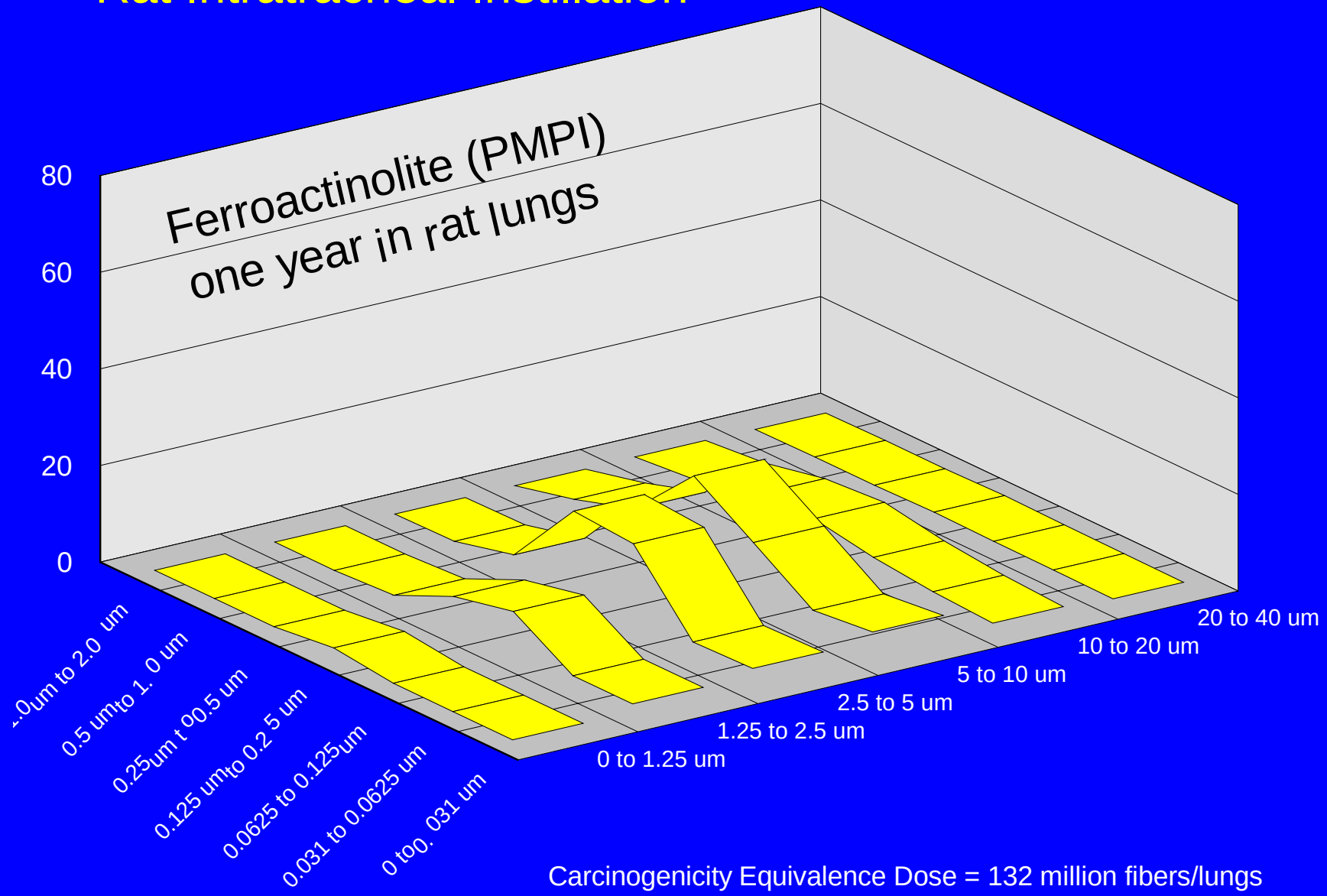
Carcinogenicity Equivalence Dose = 405 million fibers/lungs

Rat Intratracheal Instillation



Carcinogenicity Equivalence Dose = 22 million fibers/lungs

Rat Intratracheal Instillation



Carcinogenicity Equivalence Dose = 132 million fibers/lungs

Summary of fiber carcinogenicity equivalence doses (CEDs) from relative carcinogenicity factors (RCFs) based on Pott's hypothesis

Units for CEDs are millions of most potent fibers in lung per 5% tumors (IT) or in pleura per 30 % tumors (IP)

	amosite	crocidolite	ferroactinolite	ferroactinolite – one year	non-fibrous grunerite
Intratracheal	**345**	**404**	**22**	**132**	**> ?**
Intrapleural	**1149**	**539**	**72**	**441**	**> ?**

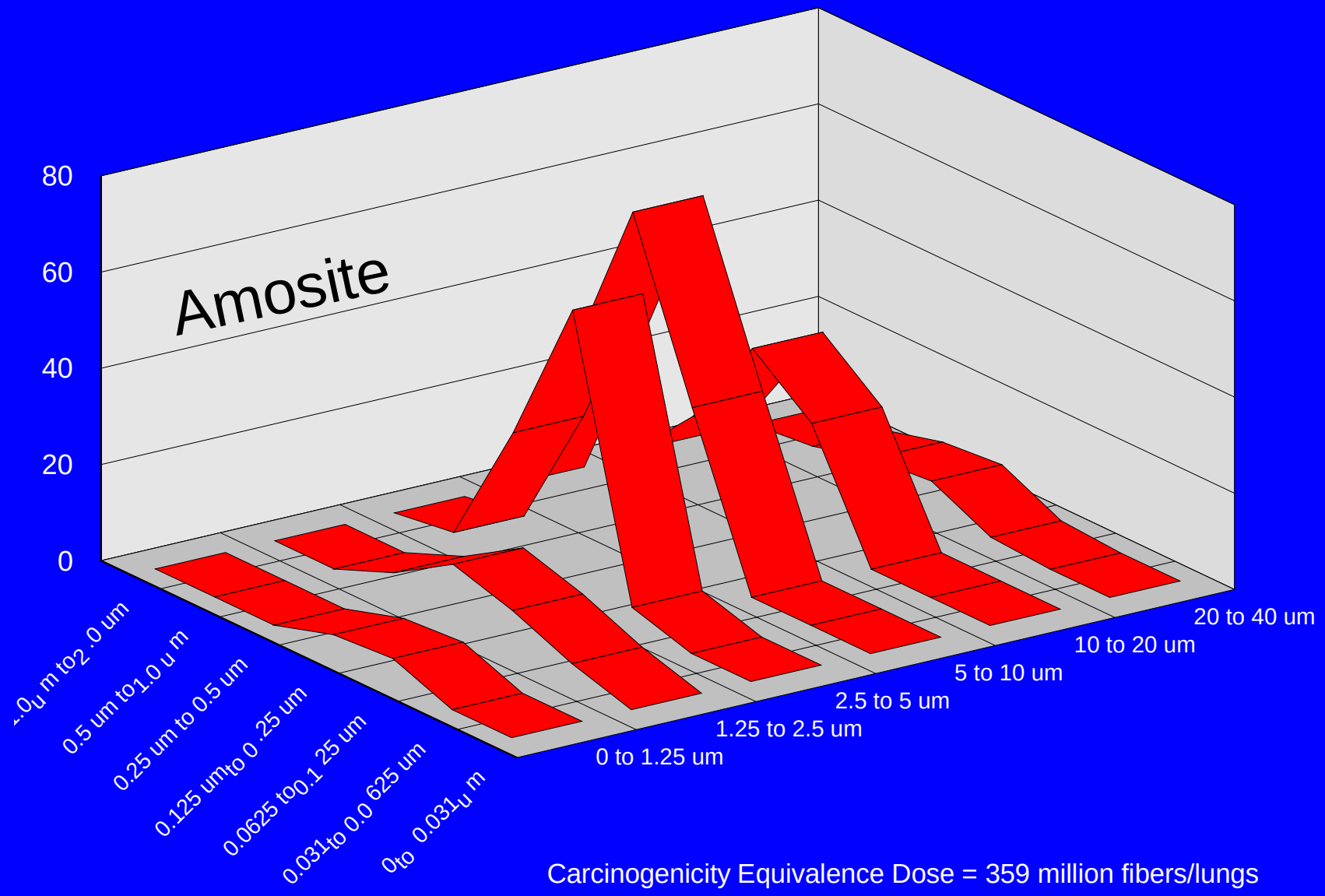
The greater the CED, the less potent the amphibole (if RCFs are accurate)

Proposal: greater RCFs for short and thin fibers than those proposed by Pott should be investigated and considered.

Adjust Relative Carcinogenicty Factors to Determine Optimum Values

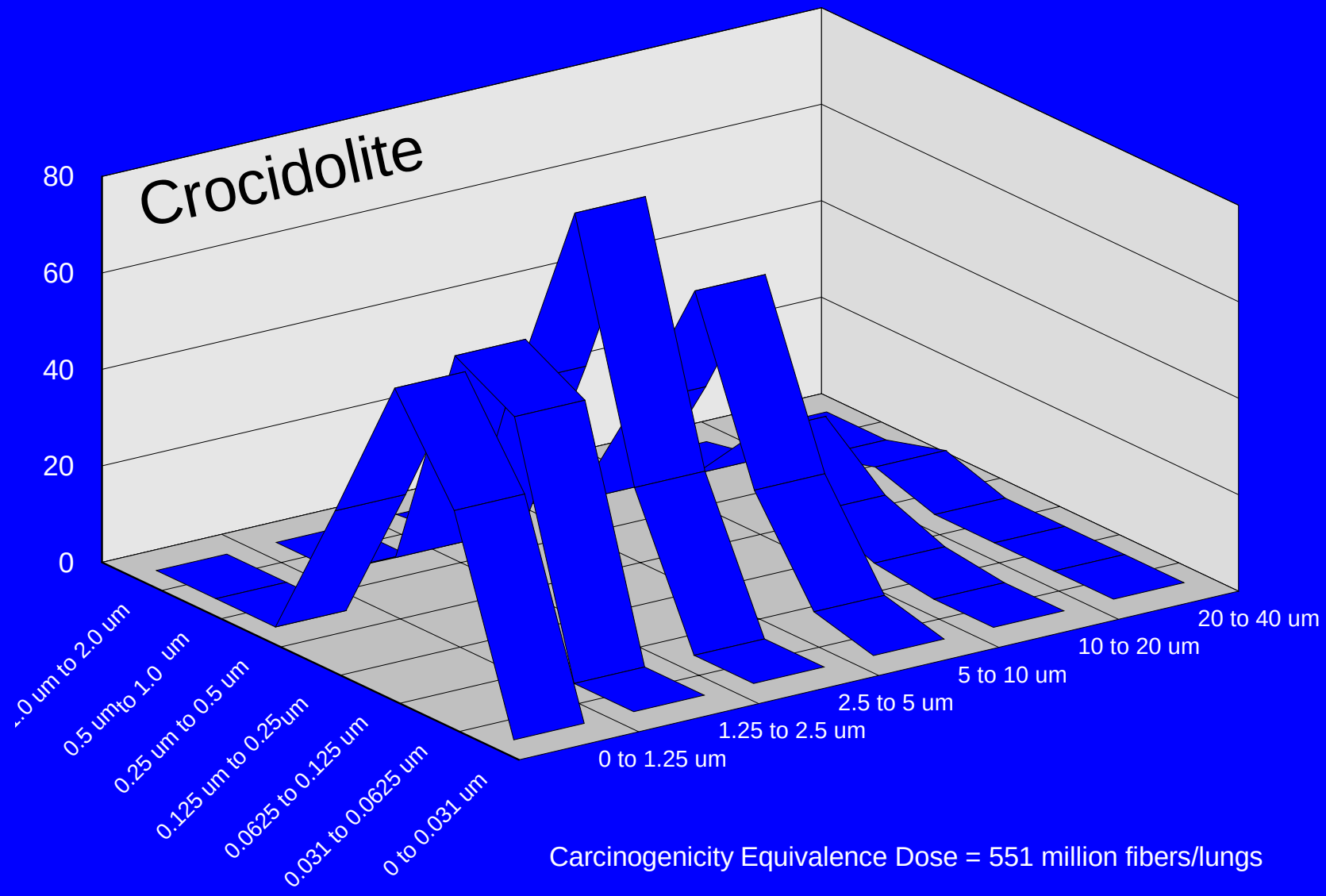
- Pott assumed short fibers have very low potencies and did not increase potency of very thin fibers.
- Cook suggests modest increase of RCFs for short, thin fibers.
- If all amphibole fibers have potencies primarily determined by fiber size and shape, carcinogenicity equivalence doses should be similar.

Rat Intratracheal Instillation



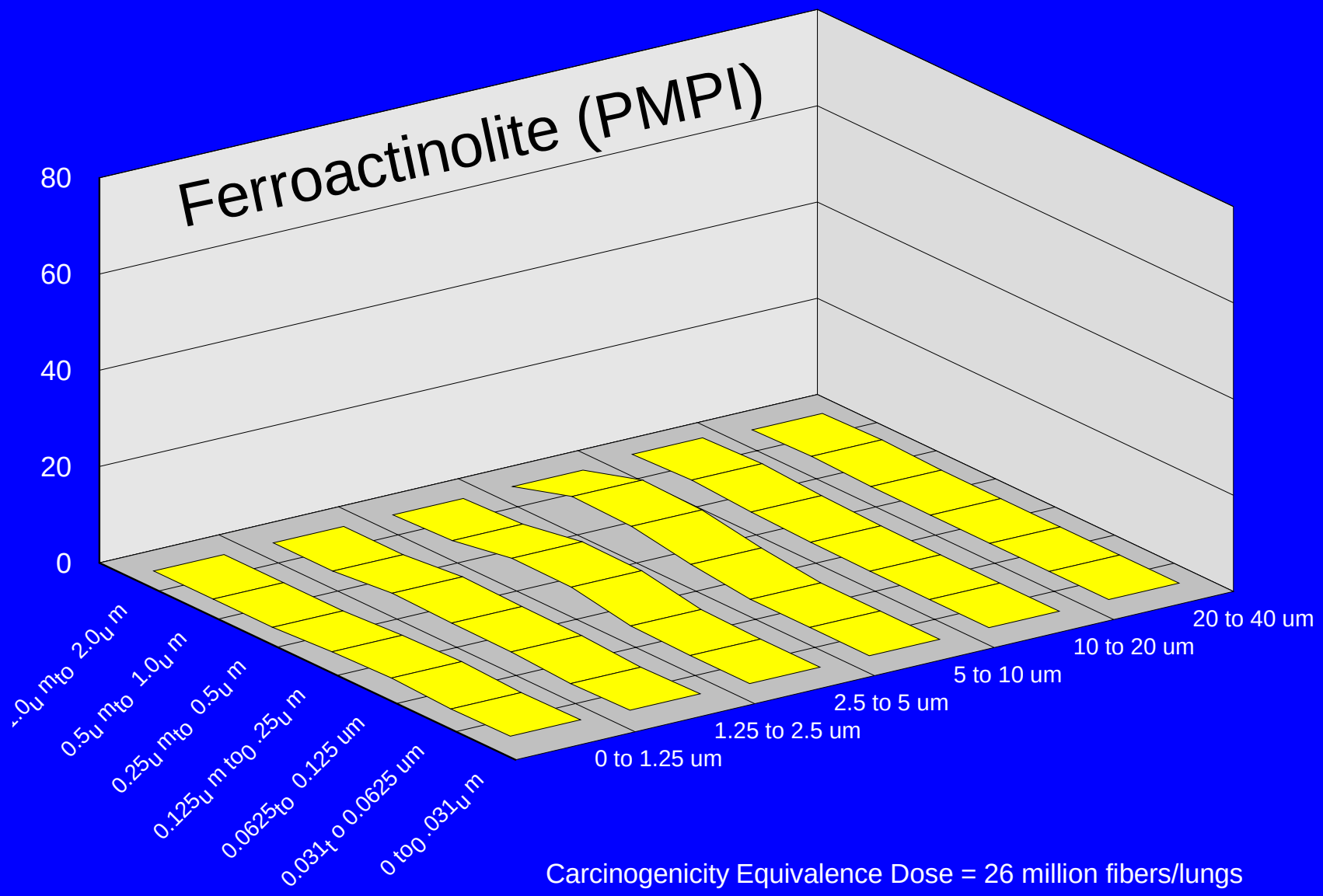
Carcinogenicity Equivalence Dose = 359 million fibers/lungs

Rat Intratracheal Instillation



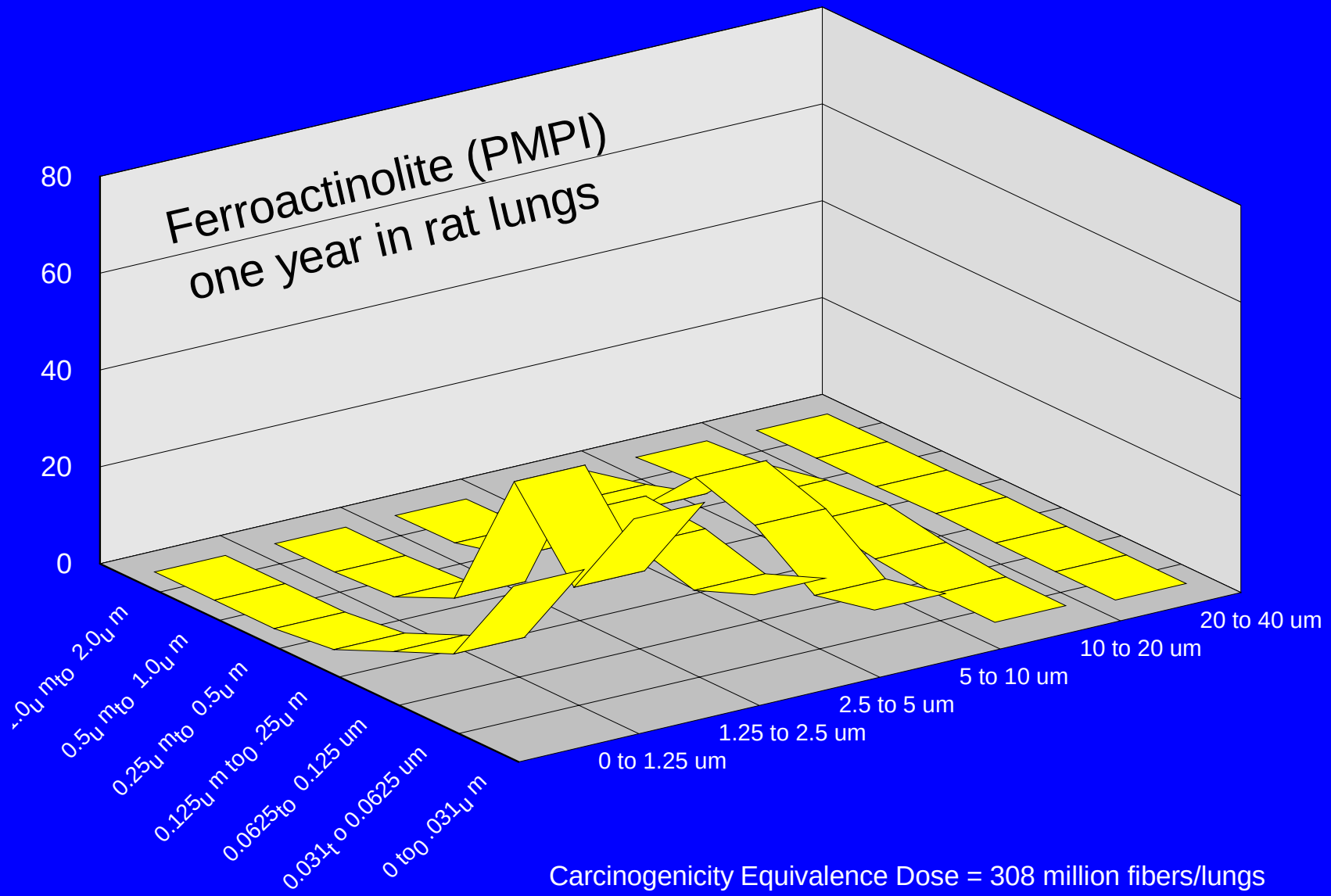
Carcinogenicity Equivalence Dose = 551 million fibers/lungs

Rat Intratracheal Instillation



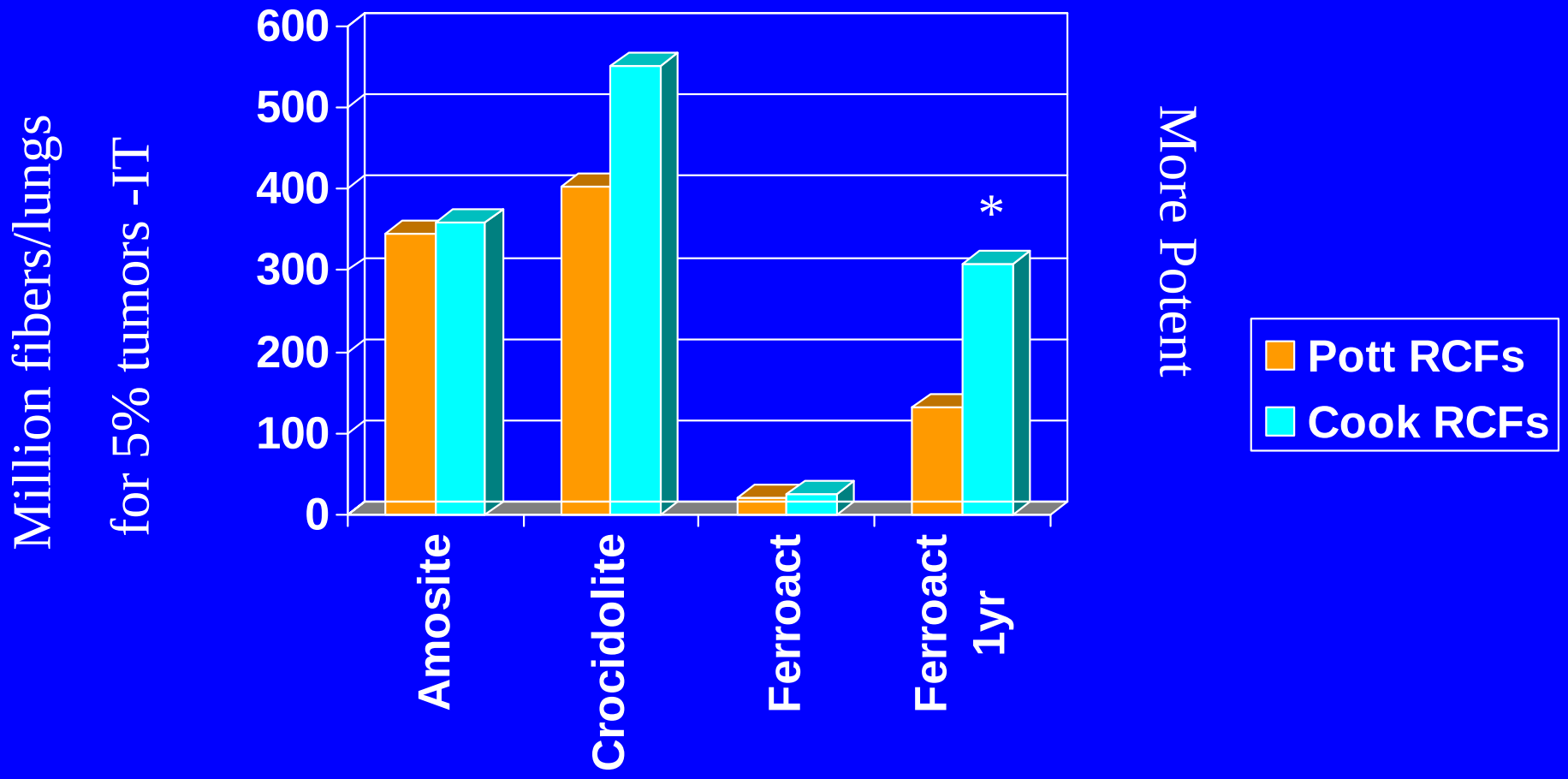
Carcinogenicity Equivalence Dose = 26 million fibers/lungs

Rat Intratracheal Instillation



Carcinogenicity Equivalence Dose = 308 million fibers/lungs

Carcinogenicity Equivalence Doses with Alternative RCFs



* For Cook RCFs, Amosite and Crocidolite CEDs at 1 year & Ferroactinolite CED at 1 year.

Conclusions

- **Fiber splitting *in vivo* greatly enhanced the potency of ferroactinolite in rat studies.**
- **Short and thin amphibole fibers appear to affect toxicity. If not, long ferroactinolite fibers would have to be regarded as many times more potent than long amosite or crocidolite fibers.**
- **Fiber numbers and sizes retained in the lung are more related to risks than the numbers and sizes of fibers inhaled. Fiber durability relates to this consideration. Fiber retention time relationships for human disease risks are uncertain.**

Conclusions continued

- **Because risk is a function of cumulative fiber dose, exposures should be measured on the basis of all fiber sizes with consideration of relative carcinogenicity and fibrogenicity of different size and shape categories.**
- **Similarly, exposure predictions should be based on all fiber sizes so that relative potencies can be included in risk assessments.**
- **Quantitative TEM analyses may be used to calibrate PLM, XRD, and other analytical methods which can not directly measure all fibers.**